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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,843	02/09/2004	Tony Peled	24024-505	9770

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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,843	PELED ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *401-463* is/are pending in the application.

4a) Of the above claim(s) *402-410,413,425-459 and 461* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *401,411,412,414-424,460 and 462* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-11-05, 08-30-06, 11-15-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant response of 11-14-2006 has been entered. With regard to restriction requirements, Applicant election of Group I drawn to claims 401, 411-412, 414-425, 434, 436-453, 455 and 460-462 is acknowledged. A further restriction was required under 35 USC § 121 in the restriction requirement filed on 10-06-2006 among groups A)-N). Applicant elected group A) drawn to nicotinamide or a nicotinamide analog. Election of the following species is acknowledged: "SCF" as a single species of cytokine, and "benzamide" as the species of nicotinamide analogs.

Claims 402-410, 413, 426-433, 435, 454, 456-495, and 463 are withdrawn from consideration as being directed to non-elected inventions pursuant to 37 CFR1.14(b), there being no allowable generic or linking claim. In addition, Claims 439-453, 455 and 461 are also withdrawn since these claims are not directed to elected species of culturing stem cells *ex vivo* in presence of nicotinamide or a nicotinamide analog. Election was made **without** traverse in the reply filed on November 14, 2006. Claims 411, 412, and 462 are examined to the extend that they read on the elected group, i.e., nicotinamide or a nicotinamide analog.

Therefore, claims 401, 411-412, 414-425, 434, 436-438, 460, and 462 are pending for examination.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be

incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner on form PTO-892 has cited the references, they have not been considered.

The information disclosure statement (IDS) submitted on 11/15/06, 08/30/06 and 11/11/05 have been considered by the examiner.

Claim Rejections - 35 USC § 112 – enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 401, 411-412, 414-425, 434, 436-438, 460, and 462 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of expanding an *ex vivo* population of CD34+ and CD34+CD38-hematopoietic stem cell in culture, while at the same time inhibiting differentiation of the said cells; said method comprising:

(a) providing hematopoietic CD34+ cells that are not enriched prior to culturing , culturing said CD34+ cell cultures *ex vivo* under conditions allowing the proliferation; said conditions for *ex-vivo* cell proliferation comprises providing a combination of cytokines selected from the group consisting of stem cell factor (SCF), TPO, FLt3, IL-6 and IL-3, and

(b) culturing said CD34+ cell cultures in presence of concentrations of 1-10 mM of exogenously added nicotinamide for up to three weeks culture period ;

thereby expanding the population of said hematopoietic stem cell while inhibiting the differentiation of said CD34+ cell cultures *ex vivo* in culture medium.

does not reasonably provide enablement for expanding any other population of stem cell or culturing said hematopoietic CD34+ cells in presence of any other condition for proliferation.

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The present invention is drawn to methods and products for in culture expansion (e.g. proliferation) of an *ex-vivo* population stem cells by down regulation of CD38, comprising reducing expression and/or activity of CD38 via CD38 inhibitors such as nicotinamide (p. 1, line 15) in order to produce transplantable hematopoietic cell preparations. CD38 is widely expressed in both hematopoietic and non hematopoietically-derived cells (p. 3, lines 10-11). Specific hematopoietic CD38 cell populations were enriched as a result of culturing hematopoietic stem cells (HSC) CD34 with nicotinamide in cultures supplemented with cytokines.

The claims when given the broadest reasonable interpretation encompass a method for expansion *ex vivo* of stem cells of any origin with any amount of nicotinamide during any period of time. The stem cell population encompasses a broad population of cells including stem cell

derived from the adult hepatic stem cells, bone marrow stroma-derived mesenchymal cells. Though Applicant's specification teaches that exposure of CD34+ cells *ex-vivo* with an amount of nicotinamide of Hematopoietic CD34+ cell cultures were initiated in the presence of a combination of 5 cytokines, SCF, TPO, FLt3, IL-6 and IL-3, with or without concentrations of nicotinamide of 1-10 mM, the specification does not adequately teach how to expand any population of stem cells while at the same time, substantially inhibiting differentiation of the stem cells *ex-vivo*.

Regarding the claimed invention to the method of expanding any stem cells ex-vivo by incubating with nicotinamide, the art teaches that incubation of highly purified hepatic stem cells cultures with concentrations of 10 mM nicotinamide for 7 days differentiates cells in a non-linage restricted manner. Specifically, Yang et al., (PNAS, 99:8078-8083, 2002) disclose that primary adult liver stem cells can differentiate into endocrine pancreas cells able to secrete proinsulin when treated with 10 mM Nicotinamide before glucose challenge (p. 8081, col. 2). Thus incubation of adult liver stem cells with Nicotinamide for 7 days induces differentiation rather than proliferation. In relation to regulation of proliferation and differentiation of an *ex-vivo* population of hematopoietic progenitor cells (e.g., phenotype $CD34^{+}$) the post filing art teaches conditions of time and concentrations of Nicotinamide resulting in proliferation but not differentiation of embryonic stem cells population. For example, Peled et al., (US2005/0054097, Date of publication March 10, 2005) teach *ex-vivo* methods of expanding hematopoietic stem cells of the CD34CD38 phenotypes from a fraction of a blood sample (p. 1, [0001 [0004]). Moreover, Peled et al., discloses conditions of culture exposure to nicotinamide allowing for extended periods of growth with no change in pluripotent status of hematopoietic stem cells (p.2,

[0017]). Similarly, Hayek et al., (WO 2005/086845, Date of publication 22-09-2005) teach a method of growing progenitor cells (p. 24, [060] for maintenance of the undifferentiated state and/or pluripotency including using a culture medium of growth factors enriched with nicotinamide in amounts varying from about 0.5 mM to about 500 mM depending on the desired result of number of cell passages (p. 3 [008] [009] and p. 35, [104] [106]). Additionally, Hayek et al., teach that different combinations of growth factors in the presence or absence of nicotinamide results in different rates of proliferation (p. 59, [184]). Hence, Hayek et al., teach a method of exposing progenitor stem cells to nicotinamide in an amount of 5mM-10mM sufficient to permit growth an maintenance of the cells in culture through multiple passages, which structural limitation are identical to that of the method used in the instant invention. Hence the state of prior art discusses that expansion and decreased differentiation of hematopoietic stem cells of the CD34CD38 phenotypes occurs, as compared to non-treated cells, by specific concentrations and exposure times to nicotinamide.

The present invention teaches the effect of nicotinamide on *ex-vivo* expansion of hematopoietic CD34+ cell cultures in the presence of a combination of cytokines for up to three weeks resulting in significant enrichment of CD34+CD38-, and CD34+-Lin- and CD34+/(HLA-DR38-) cells as compared to control cultures treated only with cytokines (p. 137, line 30 and p. 138, and 1-10). However, the as filed specification is silent about characterizing any other stem cells after incubation with nicotinamide that contributes to stem cell expansion potential.

In relation to incubating the cells with the nicotinamide analog, benzamine, the art teaches that ADP-ribosilation involves three groups of enzymes : poly(ADP-ribose) polymerase, protein mon(ADP-ribosyl)transferases, and NAD+ glycohydrolases (Rankin et al., JBC, 1989,

4312-4317). In humans, CD38 exerts NAD+ glycohydrolase activity (specification p.2 lines 23). Though all inhibitors of ADP-ribosilation, except for benzamides, share a common structural motif, the 50% inhibitory concentrations of these inhibitors of poly(ADP-ribose) synthetase activity is different and requirements for coenzyme Mg^{2+} is optional (Banasik et al., JBC, 1989, p. 1570, col. 1 and p. 1573, Table 1). Though the art consistently teach that benzamide is a potent inhibitor (Rankin et al., JBC, 1989, p. 4312, col. 1; Banasik et al., JBC, p. 1570, col. 1, paragraph 2), the art also discloses that further insight into the enzyme-inhibitor interaction is needed since some of the inhibitors such as nicotinamide and 3-aminobenzamine have proven to be mixed-type inhibitors in *in vitro* conditions (Banasik et al., JBC, p. 1570, col. 2, last paragraph).

Thus, the state of the prior at teaches that incubation of stem cells with nicotinamide preferentially contributes to differentiation or proliferation depending on the type of stem cell. For example incubation of hepatic oval stem cells with nicotinamide differentiates said stem cells into insulin-producing cells. The specification only teaches a method for expanding CD34+ and Cd34+CD38- hematopoietic stem cells in culture. Additionally, the specification does not teach how to extrapolate data obtained from $CD34^{+}$ cells *ex-vivo* culturing assay studies to the development of protocols for expanding stem cells while preventing stem cell differentiation in any other type of stem cells by subjecting said cells to amounts of nicotinamide that enhance stem cells expanding potential. Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use the claimed method of *ex-vivo* expanding stem cell potential of any stem cell by enhancing proliferation while preventing stem cell differentiation, the method comprising a step of providing any stem cell *ex-vivo* with any amount of nicotinamide insufficient for stem cell differentiation but sufficient for proliferation. Moreover, the as-filed

specification is silent about expansion of stem cells with any other nicotinamide analogs, including benzamine, thus there is not sufficient guidance to establish *ex vivo* culture conditions for concentration and incubation time with benzamine to expand a population of stem cells. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the second paragraph of 35 U.S.C. 102:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The present invention is drawn to methods and products for in culture expansion (e.g. proliferation) of an *ex-vivo* population stem cells by down regulation of CD38, comprising reducing expression and/or activity of CD38 via CD38 inhibitors such as nicotinamide (p. 1, line 15) in order to produce transplantable hematopoietic cell preparations. It is noted that the instant

claims embrace any *ex vivo* culture medium comprising nicotinamide for expanding stem cells *ex-vivo.*

Claims 401, 411-412, 414-418, 420-424 and 462 are rejected under 35 U.S.C. 102(e) as being anticipated by Brown R (US Publication No. 2002/0159984, Date of Publication October 31, 2002)

Brown R. teaches a method for *ex vivo* expansion (e.g. proliferation) of CD34+/CD38- cells derived from cord blood (p. 1, [0010]). Brown R. discloses the presence of appropriate growth factors in the medium such as interleukins, CSF, stem cell factor, thrombopoietin (TPO), interleukin-1 (IL-I) and interleukin-6 (IL-6) which influence the rate of proliferation and the distribution of cell types in the population (p. [0049]). Moreover, Brown R. discusses that many of the cytokines playing a role for driving proliferation in hematopoietic cells can be added to the culture medium at different stages of the culture to alter the cell population including FLT3, STF, IL-I, IL-6, TPO, etc. (p. [0050]) and cytokines such as, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony stimulating factor GM-CSF) (p. 4, [0049]).. Moreover, Brown R teaches the requirements for the basal medium composition for expansion of CD34+/CD38- cells *ex vivo* including nicotinamide at concentration of 4 mg/L (p. 3, col. 2, [0040] and p. 4, table I). Culture of the bone marrow CD34+ enriched population showed CD34+/CD38- cells with significant expansion at day 3, 7 and 14, in the absence of serum and low concentrations of IL-3, IL-6 and SCF (p. 10, [0119]), thus indicating expansion of the most primitive undifferentiated population of hematopoietic stem cell for use in *ex vivo* lone-term engraftment. Accordingly, the invention of claims 401,

411-412, 414-418, 420-424 and 462 are anticipated by Brown R. because the steps recited in the claims are the same as those taught by Brown R..

Claim Rejections

Provisional *Rejection, Obviousness Type Double Patenting-No secondary Refence(s)*

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 411 is provisionally rejected on the ground of nonstatutory double patenting over claim 208 of copending Application No. 10/767,064. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

Claim 411 of the instant application is drawn to an expanded population of transplantable hematopoietic cell preparation propagated *ex vivo* in the presence of nicotinamide or

nicotinamide analog, thereby inhibiting the differentiation said hematopoietic stem cell cultures *ex vivo* in culture medium.

Claim 208 of copending Application No. 10/767,064 is drawn to an expanded population of transplantable hematopoietic cell preparation propagated *ex vivo* in the presence of agents that inhibit differentiation of said cells including nicotinamide or nicotinamide analog, thereby inhibiting the differentiation of said hematopoietic stem cell cultures ex *vivo* in culture medium.

Because claim 208 of copending Application No. 10/767,064 is broadly drawn to a method for expanding hematopoietic cells in the presence of any agent including nicotinamide or a nicotinamide analog, claim 208 embraces claim 411 of the instant invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 401, 411-412, 414-425, 434, 436-438, 460, and 462 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1636; Central Fax No: (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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